Radiation recall dermatitis induced by sorafenib : A case study and review of the literature

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Abstract: BACKGROUND: Radiation recall dermatitis (RRD) is an acute inflammatory reaction confined to previously irradiated skin, mainly subsequent to the administration of certain chemotherapeutics. Here we present a rare case of RRD induced by the oral multikinase inhibitor sorafenib. CASE REPORT: A 77-year-old male with hepatocellular carcinoma was irradiated at ten different sites for bone metastases with 20-36 Gray in 5-12 fractions from January to March 2015. Sorafenib 400 mg was administered twice daily from mid-March. One week later the patient presented with fever and erythematous lesions on the right upper arm, mandible, and trunk. All skin symptoms were confined to previously irradiated areas. After RRD was diagnosed by exclusion of other causes and skin biopsy, sorafenib was paused. With the administration of topical corticosteroids and oral antihistamines, the skin reaction subsided within several days. Sorafenib was readministered after 3 weeks, which did not lead to recurrence of RRD but did cause fluctuating fever. DISCUSSION: Only four other such cases have been reported in the literature and WHO pharmacovigilance database on individual case safety reports. The current report is the first to show a potential relationship between the severity of sorafenib-induced RRD and radiation dose, histopathological features, and simultaneous acute radiation dermatitis and mucositis. CONCLUSION: RRD induced by sorafenib is a rare phenomenon, but should be considered in patients showing erythematous skin lesions 1-2 weeks after initiation of the drug, predominantly in areas where skin has been irradiated with an equivalent dose 30 Gy. Discontinuation of sorafenib with possible readministration should be evaluated with respect to the clinical situation and severity of reaction.

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Abstract (english):

Background: Radiation recall dermatitis (RRD) is an acute inflammatory reaction confined to previously irradiated skin subsequent to the administration of certain chemotherapeutics. Here we present a rare case of RRD induced by the oral multikinase inhibitor sorafenib.

Case report: A 77-year old male with hepatocellular carcinoma was irradiated at ten different sites for bone metastases with 20-36 Gray in 5-12 fractions from January to March 2015. Sorafenib 400 mg was started twice daily in mid-March. One week later the patient presented with fever and various erythematous lesions in the right upper arm, mandible and trunk confined to irradiated areas. After RRD was diagnosed by exclusion of other causes and skin biopsy, sorafenib was paused and with the administration of topical corticosteroids and oral antihistamines the skin reaction subsided within several days. Sorafenib was re-administered after 3 weeks and did not lead to re-occurrence of RRD.

Only four other such cases have been reported in the literature and WHO pharmacovigilance database on individual case safety reports. Our report is the first with a potential relation between the severity of Sorafenib-induced RRD and the radiation dose, the histopathological features, and simultaneous acute radiation dermatitis and mucositis.

Conclusion: RRD induced by sorafenib is a rare phenomenon, but should be considered in patients showing erythematous skin lesions 1-2 weeks after initiation of the drug preferentially in areas where skin has been irradiated with more than 30 Gy equivalent dose. Discontinuation of sorafenib and re-administration should be considered depending on the clinical situation.

Abstract (deutsch):

Hintergrund: Recall-Strahlendermatitis (RRD) ist eine akute Entzündungsreaktion der Haut in zuvor bestrahlten Arealen, welche meist nach Einnahme bestimmter Chemotherapeutika auftritt. Nachfolgend präsentieren wir einen seltenen Fall von RRD unter Therapie mit dem Multikinase-Inhibitor Sorafenib.

Fallbeschreibung: Ein 77-jähriger, männlicher Patient mit ossär metastasiertem hepatozellulärem Karzinom wurde zwischen Januar und März 2015 an insgesamt 10 verschiedenen Lokalisationen mit 20-36 Gray in 5-12 Fraktionen bestrahlt. Sorafenib 400 mg wurde ab Mitte März zweimal täglich verabreicht. Eine Woche später entwickelte der Patient Fieber und erythematöse Läsionen am rechten Oberarm, Unterkiefer und Rumpf. Die Hautveränderungen waren allesamt auf zuvor bestrahle Areale begrenzt. Nach Ausschluss anderer Ursachen mittels Biopsie einer der Hautveränderungen wurde die klinische Diagnose einer RRD gestellt. Sorafenib wurde pausiert und topische Kortikosteroide sowie orale Antihistaminika verabreicht, woraufhin die Hautreaktionen abklangen. Eine erneute Gabe von Sorafenib nach insgesamt dreiwöchiger Pause führte zu keiner neuerlichen Hautreaktion.

Nur vier weitere Fälle von RRD unter Sorafenib wurden bislang weltweit berichtet. Im vorliegenden Fall werden erstmals ein potentieller Zusammenhang des Schweregrads der RRD unter Sorafenib mit

der Bestrahlungsdosis der Haut, die histopathologischen Veränderungen sowie eine gleichzeitig vorliegende akute Strahlendermatitis und Mukositis dargestellt.

Schlussfolgerung: Durch Sorafenib hervorgerufene RRD ist ein seltenes Phänomen, welches als erythematöse Hautreaktion 1-2 Wochen nach Therapiebeginn mit der Substanz in bestrahlten Hautarealen auftritt. Eine Therapiepause mit möglichem Wiederbeginn von Sorafenib sollte abhängig von der klinischen Situation und dem Schweregrad der Reaktion evaluiert werden.

Background

Radiation recall dermatitis (RRD) is defined as an acute inflammatory reaction confined to previously irradiated skin occuring usually months to even years after the administration of certain drugs, mostly classical chemotherapeutics [1].

Sorafenib is an oral multikinase inhibitor and targeted anticancer substance and is indicated for the treatment of unresectable hepatocellular carcinoma (HCC), advanced I-133-refractory thyroid carcinoma or advanced, pre-treated renal cell carcinoma [2]. Most common adverse effects of sorafenib include gastrointestinal with abdominal pain, diarrhea and nausea, hepatic with elevated levels of liver enzymes and dermatologic with palmar-plantar erythrodysesthesia (hand-foot reaction), alopecia and rash [3-5]. Here we present a rare case of RRD induced by sorafenib in a patient irradiated for several bone metastases from his hepatocellular carcinoma (HCC). A systematic review of published cases in the scientific literature and the WHO pharmacovigilance database was conducted to identify risk factors, signs and course of this reaction and outcome.

Case study

A 77-year old male Caucasian (weight 67 kg, height 160 cm, BMI 26 kg/m^2) with Hepatitis C associated HCC (diagnosis in 04/2014) received radiation to several metastatic bone sites between January and March 2015. The radiation dose was 20-36 Gray (Gy) delivered in 5-12 fractions (Table 1) which resulted in a good analgetic effect with improvement of patient's mobility. Sorafenib was started at a dosage of 200 mg orally twice daily in mid-March with slow dose increments. Long-term co-medication included amlodipine, metoprolol, hydrochlorothiazide for hypertension, tamsulosin for prostatic hyperplasia, oxycodone for pain and esomeprazole for gastric ulcer prophylaxis.

One week after initiation of sorafenib the patient presented with fever (38.2°C), rising CRP (23 mg/l) and a painless erythematous lesion at the right elbow where he had been operated for pathologic fracture and had received postoperative irradiation with 12 x 3 Gy. Blood pressure, heart rate and oxygen saturation were unchanged compared to baseline values (blood pressure 150/80 mmHg, pulse rate 91/min., oxygen saturation SpO2 92%). Assuming a local skin-infection antibiotics (1 g amoxicillin / 200 mg clavulanic acid every 8 hours i.v.) were started. As per schedule, the dose of sorafenib was escalated to 400 mg twice daily and in the following days the erythema spread proximally into a distinct rectangular shape equivalent to the previous irradiation field. In addition, other skin lesions evolved, all of them in currently (acute radiation dermatitis, ARD) or previously irradiated areas (radiation recall dermatitis, RRD) (Figure 1, Table 1). RRD was suspected and sorafenib was stopped one week after the first symptoms occured. Affected skin areas included currently and previously irridated areas like mandible, humerus, scapula and spine. Multiple erythematous papules and plaques resulted in dermatitis grade 1 – 3 according to the common terminology criteria for adverse events version 4.0 (CTCAE) [6]. The severity of dermatitis showed a potential relation with the administered radiation dose, because ≥ grade 2 skin toxicity predominantly occurred when the maximal skin dose was above 30 Gy (Table 1). In addition the patient developed an urinary retention and severe mucositis CTCAE grade 2. Topical therapy of the skin lesions with corticosteroids (betamethasone, clobetasol) and systemic oral antihistamines (fexofenadine 180 mg twice daily) were

administered. Blood cultures remained negative. The patient developed a generalized eczematous skin reaction with severe pruritus. A skin biopsy of an erythematous lesion localised on the right chest revealed diffuse perivascular lymphohistiocytic infiltrate with few eosinophils in the corium and apoptotic keratinocytes and distinct vacuolisation in the junction zone (Figure 2).

The skin reaction decreased within 14 days after termination of sorafenib. After an interval of 3 weeks sorafenib was restarted in a reduced dosage of 200 mg twice daily. The skin reaction did not worsen, but the patient developed fluctuating fever, so eventually sorafenib was discontinued after another week.

Systematic Review and Discussion

We present a case of increased skin toxicity and severe mucositis shortly after initiation of sorafenib: with worsening acute radiation induced dermatitis in areas currently under treatment (acetabulum, SIJ, L1, mandible), and RRD in previously irradiated areas (scapula, humerus, T3, T6, T10, 8th rib) (see Table 1).

The radiosensitizing effect of sorafenib in combination with radiotherapy has been shown in different cell lines [7-11]. Peters et al. reported on a patient receiving sorafenib and irradiation for his lumbar metastasis of a renal cell carcinoma who died of severe bowel complications after radiotherapy [12].

In contrast to other cutaneous complications of molecularly targeted therapies such as hand-foot skin reaction, RRD induced by sorafenib is a rare phenomenon. In large clinical trials in patients with HCC, who received sorafenib in combination with radiotherapy, cases of RRD were not reported [13, 14]. Similarly, no known reactions have been reported after treatment of gliomas [15, 16], pancreatic cancer [17, 18] or sarcoma [19-21].

We performed a systematic search for RRD induced by sorafenib in MEDLINE ("radiation recall dermatitis sorafenib"; "recall sorafenib") and the WHO global database "VigiBase®" in pharmacovigilance [22]. So far, only 3 cases have been reported in the literature (Table 2). Hsieh described a RRD in a patient with HCC after intensity modulated radiotherapy (IMRT) of the liver with 48 Gy and start of sorafenib 300 mg twice daily ten days after SBRT. A well defined skin lesion at the right upper abdomen appeared 1 week after start of sorafenib and resolved 10 days after stopping the drug and local therapy with clobestasol propionate [23]. Oh and collegues observed an erythematous lesion with dry desquamation on the right chest wall in a patient with HCC, irradiated for a chest wall mass with 39 Gy. After completion of radiotherapy sorafenib was started with 400 mg twice daily and the skin lesion occurred after 14 days. Another 10 days later, the patient presented with a disseminated exanthematous rash and severe pruritus. Sorafenib was stopped and an oral antihistamine was prescribed. One week later, the symptoms resolved and sorafenib was restarted without any further skin reactions [24]. Chung et al. presented a case of a 38-year old male with liver metastases treated with palliative radiotherapy (6 x 5 Gy). Three weeks after completion of radiotherapy sorafenib was started with 200 mg twice daily. Several days later the patient presented with pruritus of the left posterior flank, hyperpigmentation and dry desquamation in the previously irradiated areas. Sorafenib 200 mg twice daily was continued and a topical steroid cream was administered. The pruritus and skin reaction resolved 2-3 weeks later. The dose of sorafenib was escalated to 400 mg twice daily. No further exacerbations of the RRD occurred [25]. In the

pharmacovigilance database only one other case of “recall phenomenon” and sorafenib was identified. Sorafenib was the only suspected drug in a 51-year old male with metastatic renal cell carcinoma. Other reported symptoms included vesicular rash, swelling, tenderness and pain. All reported patients with sorafenib associated RRD were male with a median age of 51 years and an average daily dose of 575 mg (range: 300 – 800 mg) of sorafenib. Symptoms started early after initiation of sorafenib within 1-2 weeks.

The leading symptoms in the reported cases include erythematous skin lesions localized in areas of previous radiation exposure marked by disseminated exanthematous rash, pruritus and pain. RRD caused by other chemotherapeutics occurred frequently with an interval between radiotherapy and chemotherapy of less than 2 months [26]. A dose reduction or discontinuation of sorafenib together with systemic steroid therapy, antihistamines and local treatment led to rapid improvement of symptoms. Rechallenge with the agent did not lead to symptom recurrence.

There seems to be a radiation dose dependence of the severity of RRD. In contrast to other case reports with RRD after initiation of sorafenib, our patient was irradiated at several different localisations with different radiation doses. He developed pronounced RRD in areas of the skin irradiated with a minimum of 30 Gy equivalent skin dose (see Table 1). Especially lesions near to the body surface and irradiated with 3D-conformal radiotherapy are associated with high skin doses and are therefore more prone to RRD. Radiation dose-dependent RRD has also been reported after treatment with bleomycin and docetaxel, respectively [27, 28]. Interestingly, the first occurrence of RRD in our patient was at the right upper arm, where he had received postoperative radiotherapy after osteosynthesis of a pathological humerus fracture. The RRD might have been triggered by the postoperative inflammatory environment. Other authors hypothesized that potential triggers might be impaired epithelial function induced by radiation effect on epithelial stem cells, changes in vascularization or DNA repair [29].

Sorafenib is an inhibitor of multiple intracellular and cell surface kinases. It blocks Raf kinases, which mediate cell proliferation and differentiation, and inhibits angiogenesis including vascular endothelial growth factor receptor [30]. The pathogenesis of RRD induced by sorafenib is unknown – reaching from an idiosyncratic hypersensitivity reaction, a defect in DNA repair to a direct toxic effect of the respective agent [31]. Skin biopsy, which was not performed in previous reports, demonstrated in our patient vacuolization of the dermoepidermal junction, apoptotic keratinocytes with sparse perivascular infiltrate of lymphocytes and eosinophils (Fig 2). The histological picture mimicked the pattern of graft-versus-host reactions of the skin or cutaneous drug allergies.

Radiation recall reactions followed by sorafenib might not only be confined to skin reactions; cardiotoxicitiy has also been described [32]. A patient following irradiation of her lung cancer and start of sorafenib 5 months after radiotherapy presented with edema in the basal and mid anterior wall of the heart muscle matching to the previously irradiated area [32]. In addition to augmentation of acute skin reaction sorafenib might also enhance acute mucosal toxicity. Our patient displayed enhanced mucosal toxicity in the oral cavity and the urethra with urinary retention in response to radiotherapy of the mandible and the pelvic region, which might be related to the radiosensitizing effect of sorafenib described above.

Conclusion

RRD induced by sorafenib is a rare phenomenon. The severety of the reaction seems to be radiation dose dependent (mainly after 30 Gy equivalent dose to the skin). Adverse reactions typically appear 1-2 weeks after commencing sorafenib. Besides, systemic reactions like fever and rash can also occur. RRD is a clinical diagnosis. Histologic sampling might be performed to exclude other causes of skin conditions. Therapy of RRD consists of discontinuation of sorafenib, treatment with topical steroids and/or oral antihistamines. A rechallenge with sorafenib could be considered depending on the clinical situation and grade of dermatitis on a case-by-case basis.

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Conflict of Interest:

No author has a financial or personal interest in the subject matter or materials discussed in the manuscript. Drs. SS, OR, CB, SW, Profs. BP and MG state that there are no conflicts of interest.

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Tables/Figures

RT volume	RT dose (fx x dose [Gy])	Interval end RT – begin reaction (days)	RT tech-nique	RRD/ ARD	CTCAE grade	Distance PTV/skin (min. [cm])	Max. skin dose (EQD2 (α/β=8); [Gy])
Humerus (r)	12x3*	37	3D	RRD	3	<0.5	39.4
Scapula (l)	6x5	59.	3D	RRD	2	<0.5	40.5
8.th rib (r)	5x5	40	3D	RRD	2	<0.5	30.2
T6	5x7	50	RA	RRD	0-1	2.2	28.0
T10	5x7	57	RA	RRD	0-1	1.2	25.8
T3	5x7	50	RA	RRD	0	5.0	19.8
SIJ (l)	5x4	2	3D	ARD	2	1.2	18.0
L1	5x4	2	3D	ARD	1	1.8	21.8
Mandible (l)	5x4	2	3D	ARD	1	<0.5	25.8
Acetabulum (l)	5x4	2	3D	ARD	0	5.7	8.6

Table 1: Details of all radiation treatments that led to either radiation recall dermatitis (RRD) or acute radiation dermatitis (ARD). Interval in days between end of radiation therapy and begin of the reaction. CTCAE: common terminology criteria for adverse events [6], l: left, r: right, RA: rapid arc, 3D: 3D conformal radiotherapy, *post-operative radiotherapy

Author, Year	Age, Gender	Diagnosis	Radiotherapy	Dosage of sorafenib	Onset of RRD after start of sorafenib	Symptoms	Therapy of RRD	Outcome
Stieb, 2015	77, m	HCC	Bone metastases 20-36 Gy	2 x 400 mg	1 week	• Erythematous rash, eczematous, dissemination, pruritus	• Topical steroids and oral antihistamines • Sorafenib discontinued	• Skin reaction decreased within 2 weeks
Hsieh*, 2014	63, m	HCC	Liver SBRT 6 x 8 Gy	300 mg daily	1 week	• RRD grade 2	• Topical steroids • Sorafenib discontinued	• Symptoms resolved after 10 days
Oh*, 2013	50, m	HCC	Chest wall mass 13 x 3 Gy	2 x 400 mg	2 weeks	• Erythematous patch, dry desquamation, dissemination, pruritus	• Oral antihistamines • Sorafenib discontinued	• Sorafenib was started again, no recurrent RRD
Chung*, 2010	38, m	HCC	Liver SBRT 6 x 5 Gy	2 x 200 mg	Several days	• Progressive pruritus, fatigue, patchy hyperpigmentation, dry desquamation	• Topical steroids • Sorafenib continued	• Pruritus and skin changes resolved after 2-3 weeks • Sorafenib was escalated without exacerbation of RRD
n.a.**, 2008	51, m	RCC	n.a.	n.a.	n.a.	• Vesicular rash, swelling, tenderness, pain	• n.a.	• n.a.

Table 2: Present case and summary of reported cases of RRD in *MEDLINE and the **WHO database "VigiBase®" [22]; HCC: hepatocellular carcinoma, m: male, n.a.: not available, RCC: renal cell carcinoma, RRD: radiation recall dermatitis, SBRT: stereotactic radiotherapy

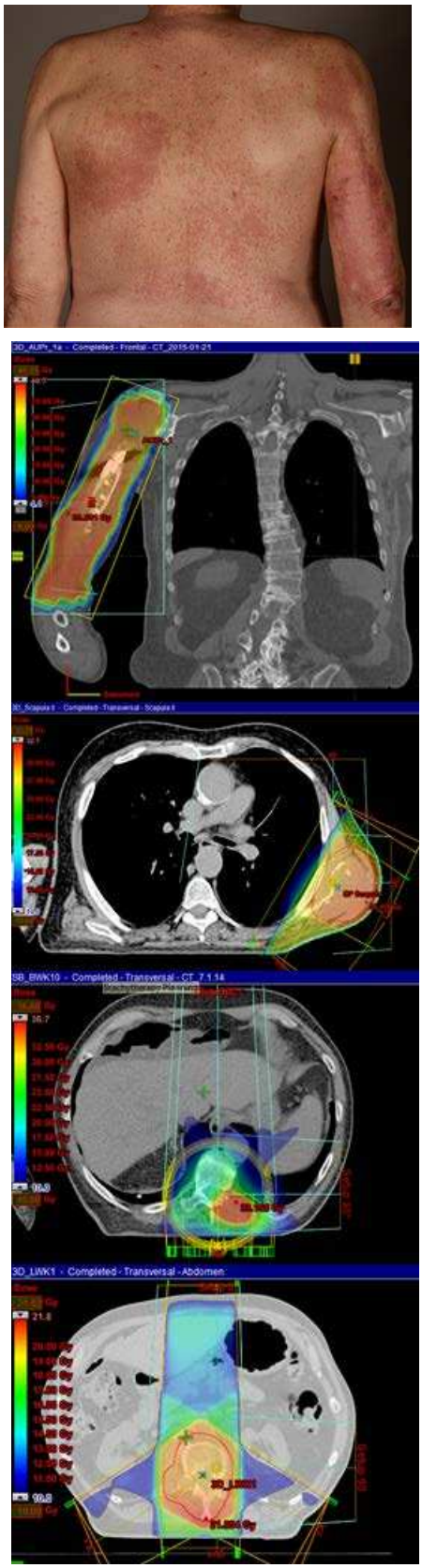

Figure 1: Correlation of radiation recall dermatitis (right humerus, left scapula, T10) and acute radiation dermatitis (L1) with radiation fields.

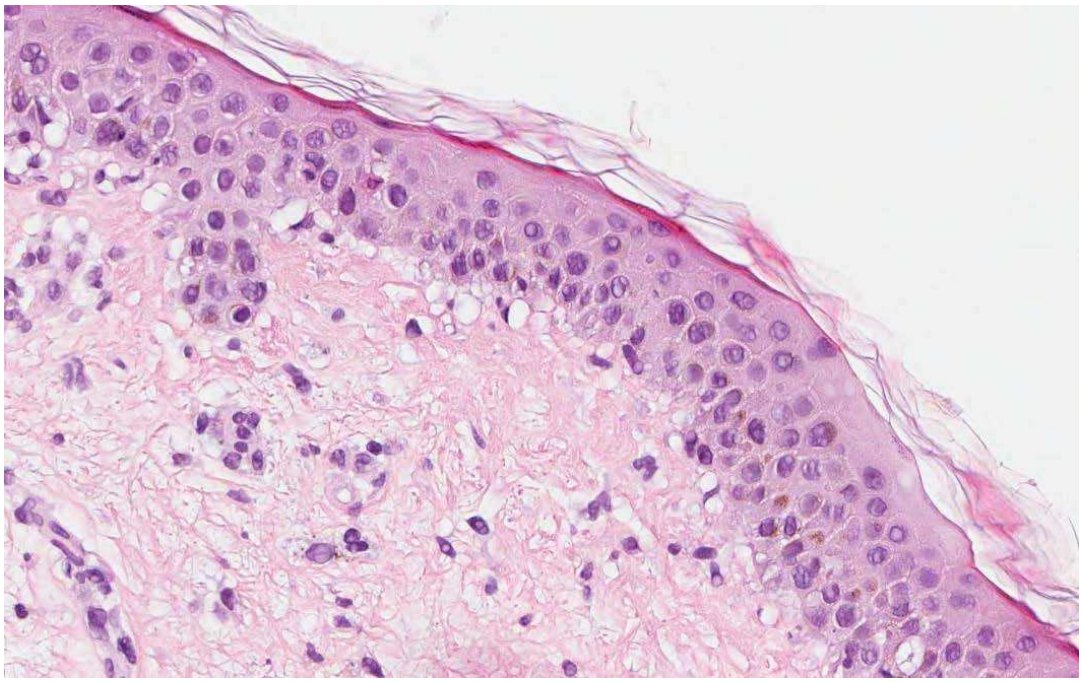

Figure 2: Punch biopsy of a lesion at the right thoracic wall. The histopathological finding revealed a vacuolization of the dermoepidermal junction, apoptotic keratinocytes with sparse perivascular lymphocytic infiltrate and few eosinophils.